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# Role of the circadian clock in fine-tuning the process of leaf senescence in plants

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ABSTRACT

Leaf senescence is a developmental process and a critical evolutionary strategy for fitness in plants, involving highly organized regulatory mechanisms. Many environmental signals as well as internal developmental aging trigger leaf senescence. Circadian clocks provide timing information for the adaptation of organisms to changing environmental conditions via dynamic metabolic and physiological regulatory networks. Interactions between aging and the circadian clock have been well characterized in animals. In plants, recent studies reveal similar interactions between leaf senescence and the circadian clock, supporting the evolutionary conservation of these interactions in both animal and plant kingdoms. In this review, we discuss the major clock components and senescence regulators that connect these two regulatory mechanisms, and the significance of this relationship in the plant life history.



## 1. Introduction

Aging is inevitable in most living organisms. Each species has a unique aging strategy. In plants, aging is associated with age-dependent senescence and death of various organs, which is critical for maintaining fitness and productivity. Leaf senescence is a representative example of age-dependent senescence. During leaf senescence, plants mobilize nutrients accumulated in leaves during the growing season via photosynthesis and nutrient uptake to the newly developing leaves or seeds [1]. Thus, proper timing of leaf senescence is a crucial process for maintaining the fitness of a population. Numerous genetic and molecular studies suggest that leaf senescence is regulated at several different levels, including chromatin, transcriptional, post-transcriptional, translational, and post-translational levels [2]. 'Omics' analyses have also expanded our understanding of the molecular regulatory mechanisms underlying the process of leaf senescence [3]. Plant-specific transcription factor (TF) families, such as NAC (NAM/ATAF1,2/CUC2) and WRKY (contains the conserved WRKY domain), serve as important regulators of aging [4–6]. This implies that aging in plants proceeds via unique regulatory pathways involving plant-specific TFs.

Among the several regulators of leaf senescence, *ORESARA 1* (*ORE1*/*ANAC092*) has been widely studied in plants. The *ORE1* gene was isolated from *Arabidopsis* while screening mutants showing dark-induced leaf senescence [7]. It encodes one of the NAC TFs, which positively regulates leaf senescence and mediates several leaf senescence pathways by regulating the expression of senescence-associated genes (*SAGs*) such as *BIFUNCTIONAL NUCLEASE 1* (*BFN1*) and *SAG29* [8]. The *ORE1* gene is located downstream of the *ETHYLENE INSENSITIVE 2* (*EIN2*) gene, which regulates the ethylene signaling pathway. The expression of *ORE1* is increased during leaf aging, leading to age-induced cell death; however, *ORE1* expression is negatively regulated by *microRNA164* (*miR164*). Thus, *EIN2*, *ORE1*, and *miR164* form a trifurcate feed-forward loop that modulates leaf senescence [9]. A recent report also suggests that EIN3, a downstream regulator of *EIN2*, is more closely involved in regulating *ORE1* expression, and constitutes the trifurcate feed-forward loop along with *miR164* and *ORE1* [10]. The circadian clock also regulates the expression of *ORE1*, suggesting the involvement of the circadian system in leaf senescence [11,12].

Almost all living organisms on earth are influenced by daily and annual environmental cycles, including light/dark cycles and temperature, caused by the rotation of the earth on its axis and its revolution around the sun. The circadian clock senses the environmental cycles and transduces this information to the endogenous circadian system, which generates proper cyclic rhythms adapted to the environment [13]. Thus, the circadian clock coordinates most biological processes with a daily cyclic rhythm. According to the circadian resonance hypothesis, organisms generate accurate endogenous rhythmicity with these environmental cycles to enhance their fitness [14]. In many organisms

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including *Arabidopsis*, a cyclic rhythm of approximately 24 h is generated via interconnected feedback loops of core circadian oscillators. In *Arabidopsis*, CIRCADIAN CLOCK ASSOCIATED 1 (CCA1), LATE ELONGATED HYPOCOTYL (LHY), PSEUDO-RESPONSE REGULATOR 7 (PRR7), and PRR9 comprise a morning loop, whereas TIMING OF CAB EXPRESSION 1 (TOC1), GIGANTEA (GI), EARLY FLOWERING 3 (ELF3), ELF4, and LUX ARRYTHMO (LUX) comprise an evening loop. Among these proteins, ELF3, ELF4, and LUX play similar roles in circadian regulation as components of the evening complex (EC) [15]. The morning and evening loops are interconnected, and generate circadian rhythmicity according to environmental cycles [16]. The circadian clock regulates many aspects of plant development and physiology throughout the life cycle [17]. Flowering is a well-known example of circadian clock regulated developmental processes. The circadian clock perceives the photoperiod length and activates CONSTANS (CO), a key flowering regulator, when the endogenous rhythm of plants coincides with the photoperiod length, according to the external coincidence hypothesis [18].

In animal models, the interaction between aging and the circadian clock is reciprocal. Aging is associated with a change in circadian rhythmicity, such as period length and amplitude of clock gene expression [19–21]; in turn, the disruption of circadian rhythm affects aging processes in several animal models. For example, mutations in *CLOCK* and *BMAL1*, core clock genes, causes age-dependent diseases including cancer and neurodegeneration in mice [22–24]. Recent reports suggest that sirtuin1 (SIRT1), a longevity factor, controls core clock regulators BMAL1 and CLOCK in an age-dependent manner. Expression of *SIRT1* decreases with aging, leading to low levels of SIRT1 and low amplitude of clock gene expression in old age [25]. Two new studies suggest that aging reprograms the circadian transcriptome [26,27]. While the expression of core clock genes is maintained at a constant level during aging, the expression of circadian oscillating genes changes with aging. The circadian clock modulates homeostasis genes in young stage and stress response genes in old stage [26]. These changes are reversed with a calorie restriction diet, suggesting that age-associated physiology can be reversed by modulating the circadian clock [27]. Thus, it is important to study the interactions between the circadian clock and aging. In this review, we summarize recent studies investigating the interactions between the circadian clock and aging in plants.

## 2. Aging affects the circadian clock

Environmental cues such as light and temperature reset the circadian rhythm of organisms daily [28]. Thus, endogenous circadian rhythmicity is measured in the absence of environmental cues. Previously, several studies in animal models have shown that the length of the circadian period is altered during aging. The circadian period is lengthened during aging in invertebrates, *Neurospora* [29] and *Drosophila* [30]. Among mammals, some rodents including hamster exhibit shortening of the circadian period with aging [31], whereas some mouse strains show lengthening of this period with age [32,33]. In humans, the circadian period is shortened with age [34]. Because the endogenous circadian period is an important parameter for enhancing the fitness of organisms, each organism may choose to lengthen or shorten its circadian period according to the surrounding environment. In *Arabidopsis*, Kim et al. (2016) have shown that the circadian period is shortened during leaf aging [35]. The authors showed that the circadian period length of each leaf varies; early emerging leaves exhibit a shorter circadian period than late emerging leaves within a single plant. Additionally, third and fourth leaves of plants of different ages exhibit shortening of the circadian period during leaf aging. Leaf aging is faster under long day (LD; 16 h light/8 h dark) conditions than under short day (SD; 8 h light/16 h dark) conditions [36]. With aging, the rate of circadian period shortening is more severe under LDs than under SDs [35]. This explains that age is tightly associated with circadian period changes in *Arabidopsis*. Among several clock mutants, only the *toc1* mutant does not show a shortened circadian period during leaf aging, indicating that TOC1 is a key clock component that links the circadian clock and aging in *Arabidopsis* [35].

## 3. Resonance between endogenous and exogenous cycles improves fitness

The circadian clock has evolved by selection force for adaption to changing environments [37]. The circadian resonance hypothesis derives from the role of the circadian clock in adaptation. According to this hypothesis, the fitness of organisms is enhanced when the endogenous circadian period is synchronized with the environmental cycle [14]. Several reports support this hypothesis in both plant and animal model systems. In *Arabidopsis*, clock mutant plants with a long or short circadian period are healthier in conditions that coincide with the endogenous cycle than in conditions with ~24 h period [38]. For example, *toc1* mutant plants have ~20 h circadian period, and exhibit greater survival and chlorophyll content than *ztl* mutant plants with ~28 h endogenous period when grown in a growth chamber with 20 h period; under ~28 h growth condition, the fitness of *ztl* mutant plants is increased compared with that of *toc1* mutants [38]. In the mouse model, deviation of the circadian period from 24 h is inversely correlated with lifespan [39,40]. The lifespan of mice with a cycle of ~24 h is increased by approximately 20% compared with that of mice with a long or short endogenous period [40]. In humans, several recent studies suggest that disruption of circadian resonance due to shift work increases the incidence of age-related diseases [41]. These results suggest that resonance of period between endogenous and environmental cycles is important for organismal aging.

## 4. Circadian components regulate leaf senescence

Investigation of leaf senescence has identified several senescence-regulating genes including clock components. The ELF3 protein, one of the components of the EC, functions as a negative senescence regulator by repressing *PHYTOCHROME-INTERACTING FACTOR 4* (*PIF4*) and *PIF5* at the transcriptional level [42]. The *elf3* mutants and *ELF3* overexpressor (ELF3-OX) plants exhibit enhanced and delayed leaf senescence, respectively, suggesting a novel function of ELF3 in regulating leaf senescence. The PIF family is a member of the basic helix-loop-helix (bHLH) TF superfamily; one of the PIF family members, PIF3, was originally isolated as a phytochrome-interacting molecule in yeast two-hybrid screening [43,44]. Initially, biological functions of PIF4 and PIF5 in hypocotyl elongation and cotyledon expansion were characterized in *Arabidopsis* seedlings, while focusing on light signaling pathways [45,46]. Later, Sakuraba et al. (2014) showed that PIF4/PIF5 regulate leaf senescence by directly activating *ABI5*, *EEL*, and *EIN3*. It was further revealed that PIF4/PIF5, EIN3, ABI5, and EEL directly activate the expression of *ORE1*, an aging regulator, thus forming coherent feed-forward loops [42].

ELF3 also functions in response to salt stress, one of the many senescence-inducing factors, through the regulation of GI and *PIF4* at the post-translational and transcriptional level, respectively [47]. The *elf3* mutants are sensitive to salt stress, whereas ELF3-OX plants are tolerant to salt stress. Additionally, the expression of many salt stress-related genes and *SAGs* is altered in *elf3* and ELF3-OX plants, suggesting that ELF3 mediates salt stress-induced leaf senescence. GI, a clock component, is the main inducer of

photoperiod-regulated flowering [48], and is involved in the salt stress response by inhibiting the activity of SALT OVERLY SENSITIVE 2 (SOS2), one of the main regulators of salt tolerance, via direct physical interaction [49]. Kim et al. (2013) have shown that GI protein is degraded under salt stress conditions, albeit via an unknown mechanism. Sakuraba et al. (2017) have shown that ELF3 interacts with GI and promotes its degradation under salt stress conditions. In addition, ELF3 influences SOS2-mediated salt stress response through GI, suggesting that ELF3 directly decreases the activity of SOS proteins [47].

In addition to ELF3, other EC components also act as negative regulators of leaf senescence [11,50]. The EC is a key component of the circadian clock; it maintains circadian rhythms, and integrates light and temperature signals for coordinating the growth and development of plants [51]. Loss-of-function mutations of EC components (*elf3*, *elf4*, or *lux*) cause similar phenotypes, such as arrhythmicity, long hypocotyl, and early flowering, regardless of day length [52–54]. The EC has been shown to regulate *PIF4* and *PIF5* expression under diurnal conditions by directly targeting the promoters of these genes in vivo [15]. Therefore, it is reasonable to speculate that all EC components induce early leaf senescence both in an age-dependent manner and in dark-induced condition. Kim et al. (2018) suggest that early flowering in EC mutants induces early leaf senescence because both these developmental processes (flowering and leaf senescence) are coupled by the circadian clock. Zhang et al. (2018) propose a molecular mechanism that explains how EC regulates phytohormone jasmonate (JA)-induced leaf senescence in *Arabidopsis*. Transcriptomic profiling analyses show that not only well-known senescence regulatory genes, such as *WRKY53*, *WRKY70*, *ORE1*, and *NAP*, but also JA signaling and response genes are up-regulated during EC-mediated leaf senescence. Consistently, *elf3*, *elf4*, and *lux* loss-of-function mutants exhibit accelerated leaf senescence phenotypes, whereas ELF3-OX lines exhibit delayed leaf senescence phenotype following JA treatment. Additionally, Zhang and colleagues showed that EC represses the expression of *MYC2*, a key activator of JA-induced leaf senescence, by directly binding to its promoter region. Genetic analyses show that the accelerated JA-induced leaf senescence phenotype of EC mutants is reverted by the introgression of *myc2*, *myc3*, and *myc4* mutations [50]. Collectively, these data indicate that a core circadian complex represses leaf senescence by directly binding to the promoter regions of genes involved in light and JA signaling pathways.

Two morning loop components of the circadian clock, CCA1 and PRR9, also coordinate leaf senescence in *Arabidopsis* [11,12]. Song et al. (2018) showed that *cca1* and *lhy* single mutants exhibit accelerated leaf senescence phenotypes compared with the wild type under LD conditions, and the early senescence phenotype was exacerbated in *cca1lhy* double mutants. Interestingly, the early senescence phenotype of *cca1* and *lhy* mutants is exaggerated when the LD photoperiod is changed to day-neutral (DN; 12 h light/12 h dark) photoperiod, suggesting that CCA1/LHY-mediated leaf senescence could be altered by different photoperiods. Bioinformatics screening of *SAG* promoter sequences revealed the enrichment of two well-known circadian-related cis-elements, including CCA1-binding site (CBS; AAMAATCT) and evening element (EE; AAAATATCT). *ORE1* and *GOLDEN2-LIKE 2* (*GLK2*), a chloroplast activity maintainer, exhibit oscillating expression patterns and harbor putative CBSs in the promoter regions. Additionally, CCA1 negatively regulates leaf senescence by repressing *ORE1* expression and activating *GLK2* expression by directly binding to the promoter regions of these genes.

Most recently, Kim et al. (2018) showed that PRR9 positively regulates leaf senescence via the circadian control of *ORE1*. The authors examined age-dependent leaf senescence in clock mutants to determine interactions between the circadian system and leaf senescence. Results showed that the leaf senescence phenotype of many clock mutants is altered; however, this alteration is tightly correlated with flowering, suggesting that the circadian clock regulates leaf senescence and flowering simultaneously. Among several clock mutants, only the *prr9* mutant showed delayed dark-induced senescence compared with the wild type. However, no delayed senescence (aging) phenotypes of circadian mutants have been reported in animals [55,56]. This suggests a fundamental difference in the interplay between senescence and circadian system in plants vs. animals; plant senescence requires a functional circadian system, while animal aging results from disruption of the circadian system. They also found that many senescence-related genes encoding TFs such as NAC and WRKY exhibit circadian expression patterns. Among these genes, *ORE1* is negatively regulated by the clock-controlled *miR164*, a post-transcriptional repressor of *ORE1*, suggesting that post-transcriptional regulation via miRNAs in the circadian clock system is a general regulatory mechanism in both plants and animals [57]. Furthermore, PRR9 promotes cyclic transcription of *ORE1* directly by binding to the *ORE1* promoter region, and indirectly via the suppression of *miR164*.

## 5. Perspectives and future issues

In this review, we summarized the molecular mechanisms underlying the interaction between the circadian system and leaf senescence in *Arabidopsis*. Recent studies have enhanced our understanding of the relationship between leaf senescence and clock components, and initiated a new phase of clock function research in the aging process. Circadian oscillators maintain ~24 h rhythm in cells, tissues, organs, and organisms for the adaptation to and anticipation of diurnal environmental cycles. Leaf aging changes the circadian period, and TOC1 is involved in this regulation, implying that aging information is transmitted to the circadian system via TOC1. However, we do not yet understand why the circadian period changes with aging. One possible reason is that misalignment between the endogenous rhythm and 24 h environmental cycles is associated with a physiological cost, which affects longevity [40]. Another possibility is that the lengthening or shortening of circadian period triggers age-associated physiological processes via a species-specific strategy. We suggest that the dissonance of the period between endogenous and environmental cycles triggers leaf senescence. Further molecular, genetic, and physiological analyses are required for elucidating the regulatory mechanisms and biological significance of age-dependent period shortening in *Arabidopsis*.

A variety of biotic and abiotic environmental stresses, such as drought, shade, high salinity, nutrient toxicity and deficiency, pollution, and microbial attacks, induce senescence [1]. Most of the phytohormone-regulated signaling networks play critical roles in the response of plants to these environmental changes [58]. Moreover, leaf senescence processes are interwoven with complicated crosstalk among phytohormones, including JA, abscisic acid (ABA), salicylic acid (SA), ethylene, gibberellin (GA), cytokinin (CK), and auxin [1]. The circadian clock provides plants with an adaptive advantage for responding to these environmental changes by regulating phytohormone biosynthesis and signaling pathways, and many clock components are involved in these regulations [59]. Therefore, it is possible that circadian clock components regulate leaf senescence through hormonal signaling. Zhang et al. (2018) provide substantial evidence supporting the role of EC in the regulation of JA-induced leaf senescence. Further studies are needed to understand the molecular mechanisms employed by clock components for the coordination of stress-induced leaf

senescence via hormonal regulation.

Recent studies in *Arabidopsis* show that all senescence-associated clock components regulate leaf senescence via ORE1, which suggests ORE1 as a novel molecular hub that links circadian components with leaf senescence processes (Fig. 1). Most senescence regulatory mechanisms involving ORE1 form trifurcate feed-forward pathways (Fig. 1), which are required for fine-tuning leaf senescence. In addition, CCA1 and PRR9, two morning clock components, act as negative and positive regulators of *ORE1* expression, respectively [11,12]. *ORE1* expression peaks twice (once during the day and again during the night) under LD conditions but only once (during the day) when transferred from LD to constant light (LL) conditions [11], indicating that the circadian clock is responsible for the day-time peak of *ORE1* expression. However, the exposure of plants to DN growth conditions following LL reduces the intensity of day-time peak of *ORE1* expression compared with that of night-time peak [12], suggesting that the circadian clock tightly regulates *ORE1* expression under different photoperiods, which facilitates the adaptation of plants to seasonal changes and ensures appropriate aging. Over the last few decades, many studies have been conducted to discover aging regulators, which sense the passage of time and control developmental transitions at the appropriate time. ORE1 is one such aging regulator; *ORE1* transcript levels are not only gradually increased by EIN3 and *miR164* during aging but also dynamically regulated by the circadian clock during the day (Fig. 1). The circadian clock is an endogenous self-sustained mechanism that measures the passage of time and affects developmental processes such as flowering and leaf senescence in plants; thus the circadian clock is a potential candidate for aging regulators. Understanding the mechanisms of leaf senescence by exploring the regulatory relationships among these aging regulators will provide further insights into the aging process.

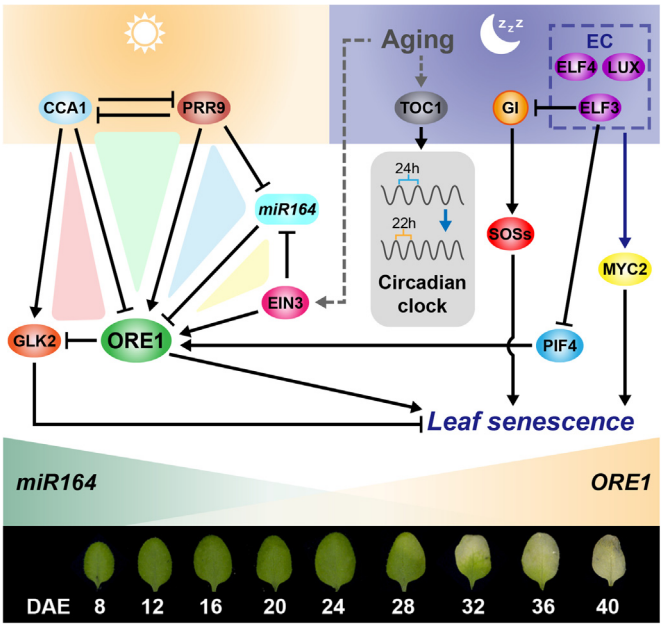


**Fig. 1. Reciprocal interaction networks between the circadian clock and aging in *Arabidopsis*.** Many circadian components are involved in the regulation of leaf senescence in *Arabidopsis*. The evening complex (EC) regulates jasmonate-induced leaf senescence by controlling *MYC2* expression. ELF3, a component of EC, negatively affects *ORE1* expression by repressing *PIF4*. ELF3 also plays a role in salt-induced leaf senescence together with GI by regulating the SOSs. A trifurcate feed-forward pathway, comprising EIN3, *miR164*, and ORE1, regulates leaf senescence. CCA1 negatively regulates *ORE1* expression, and forms two kinds of trifurcate feed-forward pathways with GLK2 or PRR9, and PRR9 forms another trifurcate feed-forward pathway with ORE1 and *miR164*. Reciprocally, the aging signal integrates with the circadian clock through TOC1, one of the core oscillators, resulting in the shortening of the circadian period with leaf aging. Colored triangles surrounded by regulatory lines indicate trifurcate feed-forward pathways.

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## Appendix A. Supplementary data

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